Remarks

In view of the above amendments and the following remarks, reconsideration of the outstanding office action is respectfully requested.

By the above amendments, claims 1, 15, 18, and 19 have been amended and claim 17 has been cancelled. The amendments to claim 1 are supported in the application, where use of the known SELEX procedure is described as a means for preparing the first pool of RNA ligands as claimed. Claim 15 has been amended to recite the limitations of original claim 17. The dependency of claims 18 and 19 has been amended in view of the cancellation of claim 17. No new matter has been introduced by these amendments. Claims 1-15 and 18-22 remain pending.

Applicants would like to thank Examiner Thomas for the courtesy extended to the undersigned representative during the telephone interview held on May 22, 2007. The substance of the interview is summarized below in the discussion of the bases of rejection. Applicants acknowledge that the SELEX procedure can be used to prepare the first pool of ligands as presently claimed; however, applicants submit that SELEX, *per se*, is not required. The SELEX procedure is merely exemplary and preferred.

As stated in the paragraph bridging pages 10-11 of the present application and as discussed during the above-noted interview, in a SELEX experiment genetic selection is applied directly to populations of RNA molecules that possess both genotypes (a sequence) and phenotypes (a binding activity that varies according to sequence). The conventional SELEX method attempts to recapitulate the natural Darwinian evolution process, in which the selection is based on phenotype (e.g. binding capability possessed by a folded RNA) and amplification is based on genotype (base pairing during PCR). While the fitness of molecules (their ability to be enriched) may be also affected by their relative efficiency of enzyme-mediated replication, this is intentionally minimized, rather than explored, in the process of the experiment in order to keep the selection pressure solely on the phenotype. The nucleotide sequence of a nucleic acid molecule, as the physical embodiment of the information encoded therein, can be used itself as the criterion for either positive or negative selection. This feature has been explored in some molecular computation experiments to solve hard combinatorial optimization problems. But when a sequence functions as the genotype of an organism, it is normally not accessible and subject to selection; and when it acts as the genotype of an aptamer in an ideal "single target selection," it is unknown until it is enriched according to its phenotype to the point of its identification. Once the sequence of an aptamer is identified in such an experiment, it loses its value of being a selection criterion

for itself, since by then the selection has achieved its practical goal and is considered finished. The present invention provides a scheme of negative selection according to genotype, which utilizes the sequence information to reduce the relative size of particular aptamer populations during the process of selection against multiple targets. More specifically, it allows the resumption of selection and amplification to identify less abundant aptamers to other targets once an aptamer family is identified due to its high growth rate.

As discussed below, none of the cited art teaches the substantial reduction or elimination of predominant species of aptamers from a selected pool, which will then allow non-predominant species in that selected pool to be identified in subsequent steps.

The rejection of claims 1, 2, 4, 7-11, 14, and 15 under 35 U.S.C. § 102(b) as anticipated by U.S. Patent No. 5,792,613 to Schmidt et al. ("Schmidt") is respectfully traversed.

Schmidt teaches a method for selecting an RNA aptamer that binds a nucleic acid molecule by way of shape recognition. According to this method, a large RNA population is pretreated with a sufficient quantity of blocking oligodeoxynucleotide to preclude potential base pairing interactions between RNA molecules in the population and the selecting nucleic acid molecule. After pretreatment, the candidate RNA population is subjected to a selection process whereby it is first contacted with the selecting nucleic acid molecule to allow non-covalent binding of the RNA aptamer to the structural element of the selecting nucleic acid molecule. The resulting RNA aptamer:nucleic acid molecule complex is then separated from the remaining free RNA molecules, after which the complex is dissociated. The selected RNA population is thereby enriched for RNA aptamers that bind the selecting nucleic acid molecule by way of shape recognition. Successive rounds of selection are carried out until at least one characteristic sequence motif becomes apparent, that is, until one specific aptamer sequence or a family of aptamers dominates the pool of selected aptamers. After each round of selection, the selected RNA population, enriched for the RNA aptamer of interest, is preferably reverse transcribed to cDNA, amplified, then transcribed into RNA before beginning the next round of selection. As discussed during the interview, this is a modified form of the SELEX procedure.

As asserted in applicants' last response and during the above-noted interview, the presently claimed invention covers a process that begins where the modified SELEX process of Schmidt ends (i.e., with an enriched pool of RNA that contains a predominant RNA aptamer species or family). While Schmidt teaches the step of "preparing" as recited in claim 1, Schmidt does not teach the "treating" step recited in claim 1.

The PTO, at pages 2-4 of the outstanding office action, repeatedly cites the discussion in Schmidt that appears in columns 2-3. However, it is clear in step (c) of Schmidt that this negative selection step results in a by-product that is no longer used by Schmidt. Moreover, the use of a blocking oligonucleotide in Schmidt as a negative selection does not have the affect of deleting predominant species; it simply precludes hybridizing nucleic acids from ever being selected and amplified, i.e., from becoming a predominant species in the first pool. These are entirely distinct of the negative selection employed in the presently claimed invention, because neither of these steps involve "treating the first pool of RNA ligands under conditions effective to reduce the concentration or eliminate the presence *of the one or more predominant target-binding RNA ligands* from the first pool of RNA ligands" (emphasis added). Schmidt is therefore deficient in this respect. As a consequence, Schmidt cannot teach the subsequent "amplifying" and "identifying" steps as recited. For these reasons, Schmidt clearly does not anticipate the method recited in claim 1, or claims 2, 4, 7-11, and 14 dependent thereon.

Because claim 15 has been amended to recite the limitations of claim 17 (which was not rejected over Schmidt), claim 15 is allowable in its present form.

In view of the foregoing, the rejection of claims 1, 2, 4, 7-11, 14, and 15 under 35 U.S.C. § 102(b) as anticipated by Schmidt is improper and should be withdrawn.

The rejection of claims 1, 2, 4, 7-11, 14, and 15 under 35 U.S.C. § 102(b) as anticipated by U.S. Patent No. 5,582,981 to Toole et al. ("Toole") is respectfully traversed.

Toole teaches a method to determine an oligonucleotide sequence which binds specifically to a target. This method is basically a modification of the SELEX procedure, whereby the oligomers (of the initial pool) contain portions that permit amplification. The process involves providing a mixture containing the above-described oligomers and incubating the oligomer mixture with the target substance coupled to a support to form complexes between the target and oligomers bound specifically thereto. The unbound members of the oligonucleotide mixture are removed from the support environment and the complexed oligonucleotide(s) are recovered by uncoupling the target substance from the support. The recovered oligonucleotides are amplified, and the recovered and amplified oligonucleotide(s), which had been complexed with the target, are then sequenced. Thus, Toole merely teaches a modified SELEX procedure.

The method of claim 1 of the present application is distinguishable from the modified SELEX procedure taught by Toole. While Toole teaches the "preparing" step as recited in claim 1, Toole is otherwise deficient because this reference in no way teaches or suggests a negative selection step applied to the enriched aptamer pool. Specifically, Toole

fails to teach the "treating" step and the subsequent "amplifying" and "identifying" steps of claim 1. For these reasons, Toole clearly does not anticipate the method recited in claim 1, or claims 2, 4, 7-11, and 14 dependent thereon.

Because claim 15 has been amended to recite the limitations of claim 17 (which was not rejected over Toole), claim 15 is allowable in its present form.

Accordingly, the rejection of claims 1, 2, 4, 7-11, 14, and 15 under 35 U.S.C. § 102(b) as anticipated by Toole is improper and should be withdrawn.

The rejection of claims 3, 5, 6, 12, 13, and 17-22 under 35 U.S.C. § 103(a) for obviousness over Schmidt in view of U.S. Patent No. 6,344,321 to Rabin et al. ("Rabin") is respectfully traversed.

The teaching and deficiencies of Schmidt are recited above.

Rabin is directed to methods for generating nucleic acid ligands to HGF and c-met using the SELEX process for ligand generation. Figure 2 of Rabin illustrates RNaseH cleavage primers used in hybridization truncate SELEX. Basically, RNaseH cleavage primers are used simply to remove the known 5'- and 3'-terminal nucleic acid sequences from the randomized aptamer sequence selected during the SELEX procedure.

Even if one of ordinary skill in the art were to combine the teachings of Schmidt and Rabin, the combination would not teach the claimed subject matter. Unlike Rabin, the RNaseH treatment in accordance with the claimed invention is used to destroy the predominant aptamer species/family from a particular SELEX pool (i.e., an unwanted RNA aptamer). The PTO acknowledged during the interview that Rabin does not teach using RNaseH in this manner. Thus, Rabin fails to both overcome the above-described deficiencies of Schmidt and teach the use of RNaseH as recited in claims 12, 13, 15, and 18.

Accordingly, the obviousness rejection of claims 3, 5, 6, 12, 13, and 17-22 is improper and must be withdrawn.

In view of all of the foregoing, it is submitted that this case is in condition for allowance and such allowance is earnestly solicited.

Respectfully submitted,

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